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ORIGINAL ARTICLE

CANCER INNOVATION

Evaluation of quality of clinical management of neuroendocrine tumors

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Abstract

Background: Neuroendocrine tumors (NETs) are a group of biologically and clinically heterogeneous neoplasms predominantly found in the gastrointestinal and bronchopulmonary tractus. Despite a rising incidence, implementation of evidence-based standardized care for this heterogenous group remains challenging. The European Neuroendocrine Tumor Society regularly reviews guidelines regarding diagnostic and treatment strategies for NETs. The aim of this study is to shed light on the care of patients with a NET in Belgian Limburg, to provide data as a basis for future studies and to check whether data and results are according to consensus guidelines and outcomes described in literature.

Methods: Our study concerned a detailed observational data collection of two large Belgian hospitals (Jessa Hospital Hasselt and Hospital Oost-Limburg Genk) with special interest in patient profile, quality of pathology reports, use of diagnostic imaging, and overall survival. Data on 188 patients were assembled between January 2010 and December 2014 with follow-up until June 2016 (median follow-up: 33.6 months).

Results: Fifty percent of patients were male. NETs were located mainly in the digestive tract (63.8%) and lung (20.2%). Appendiceal NETs were diagnosed at a significantly younger age than other tumors (41.3 vs. 64.0 years). Overall, a mean pathology report quality score of 3.0/5 was observed with the highest scores for small bowel NETs. Diagnostic and nuclear imaging was performed in 74.5% and 29.8% of cases, respectively. Seventy-four percent of the population survived until the end of the observation period with highest survival rates for appendiceal and small bowel NETs.

Abbreviations: BP-NET, bronchopulmonary neuroendocrine tumor; CD56, neural cell adhesion molecule; ENETS, European Neuroendocrine Tumor Society; FDG-PET, fluorodeoxyglucose-positron emission tomography; GEP-NET, gastrointestinal neuroendocrine tumor; MTB, medical tumor board; NET, neuroendocrine tumor; SRS, somatostatin receptor scintigraphy; TAM, time from pathology to first multidisciplinary tumor board.

Conclusion: Overall, epidemiological results were comparable with findings in the literature. Gastrointestinal NETs met most of the requirements of qualitative pathology reporting and diagnostic imaging as listed in the European Neuroendocrine Tumor Society consensus guidelines. However, consensus with regard to bronchopulmonary NETs is still scarce and remains an objective for future research. Moreover, discussing treatment strategies in specialized multidisciplinary tumor boards would facilitate regional care.

KEYWORDS

neuroendocrine tumors, epidemiology, quality, pathology report, Ki67, overall survival, guidelines

1 | INTRODUCTION

Neuroendocrine tumors (NETs) are a rare group of biologically and clinically heterogenous neoplasms. Nonetheless, its incidence has significantly risen over the last 40 years to 6.98 per 100,000 [1]. This can mainly be attributed to improved diagnostics and specialist awareness [2]. NETs are predominantly found in the gastrointestinal and respiratory system, but can occur throughout the entire body. NETs are in general characterized by their capability to produce and secrete hormones, which can cause functional neuroendocrine syndromes. However, most NETs cause only few symptoms and mimic nonmalignant diseases [3]. This frequently leads to delayed diagnosis and treatment.

Despite the introduction of guidelines in 2005, epidemiological, diagnostic, and therapeutic data remain scarce. Therefore, implementation of routine care for these patients has been difficult. The European Neuroendocrine Tumor Society (ENETS) regularly publishes and updates consensus guidelines regarding diagnostic and treatment strategies of NETs. However, elaborate data collection and further research are paramount to improve standard of care. The aim of this study was to shed light on the care of patients with a NET in Belgian Limburg and to assess whether our data are according to international guidelines and clinical practice.

2 | MATERIALS AND METHODS

2.1 | Patient inclusion and data acquisition

Patients diagnosed with a NET between January 2010 and December 2014 in Jessa Hospital Hasselt and Hospital Oost-Limburg (ZOL) Genk were identified using specific search terms provided by two specialized pathologists. This resulted in a total of 434 patients. All patients without NET or a definite pathologic confirmation were excluded, as well as patients with small-cell lung cancer. Ultimately, 188 patients were included in the study (Hospital 1: 93; Hospital 2: 95).

Files were reviewed and data were acquired by two trained medical students (K. K. and H. B.). Demographics, clinicopathologic characteristics, and data concerning early outcome were collected prospectively, and reviewed and analyzed retrospectively. The quality of data collection was assessed by random revision of the data and patients' files by two experienced NET specialists. This study followed the Strengthening The Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines [4].

The quality of the pathology reports was based on the documentation of proliferation index (Ki67), WHO classification, TNM staging (ENETS guidelines 2012 and 2016 [5–10, 11–14]) lymphangiographic invasion and markers of neuroendocrine pathology (chromogranin A, neuron-specific enolase, synaptophysin, neural cell adhesion molecule [CD56]). Every marker was awarded 1 point in this score. Each report was given a score between 0 and 5 and indicates adherence to ENETS recommendation guidelines (ENETS guidelines 2012 and 2016 [15, 16]). Patients were followed until June 30, 2016 (median follow-up: 33.6 months, range: 21–2749) and overall survival was assessed as primary endpoint. General practitioners were contacted in case patients did not receive follow-up in the hospital. Only 23 patients were lost to follow-up.

This study was approved by the institutional review board and ethics committee, conform national privacy legislation, and conducted according to the revised version of the Declaration of Helsinki. The need for informed consent was waived given the retrospective character of the study.

2.2 | Statistics

Multiple imputation (MI) was adopted to handle the incompleteness in the data called missingness. This approach has been accepted by the European Medicines Agency for application in clinical trials. MI [17–20] consists of three steps. In the first or imputation step, the principle is to replace missing values with M copies or so-called imputations. These are drawn from the predictive distribution of what is missing, given what is observed. The modeler obtains M completed datasets. In the second or modeling step, each of these is analyzed separately as if the data were complete. Thus, M estimates of the model parameters are obtained. In the third or analysis step, these M estimates are combined into a single set of parameter and precision estimates, using so-called Rubin's rules. The NET dataset is imputed using a fully conditional specification approach [19]. M imputed datasets were generated and appropriate combination rules were applied for all analyzes in the final step of MI [18]. Furthermore, linear, logistic or survival regression was applied to assess the association between the response and independent variables, depending on the type of the response variable. Based on the original data and explorative data analysis (histogram, boxplot, normal probability plot) no deviation from normality was observed. After combining the results from the completed datasets, the Wald χ^2 and type-III ANOVA F tests were applied to test the significance of the association. Of note, if the response and independent variables had no missing data, the same F test was applied without using the combination rule. Results will be presented as means with standard error unless otherwise indicated.

For survival analysis, the accelerated failure time model was selected as it is a parametric model that accounts for censoring and is considered the most accurate in the context of MI for independent variables with missing data.

All statistical analyses were conducted with SAS® (version 9.4, SAS Institute).

TABLE 1 Patient and tumor characteristics.

	No. (%)	*p* value
Tumor location ($n = 188$)		
Appendix	32 (17.0)	
Colon incl. rectum	28 (14.9)	
Lung	38 (20.2)	
Pancreas	18 (9.6)	
Small bowel	31 (16.5)	
Age (years, mean/SE)	59.8/1.33	
Appendix	41.3/2.89	
Colon incl. rectum	64.4/3.09	
Lung	64.9/2.65	
Pancreas	62.1/3.86	
Small bowel	62.7/2.94	
Sex		0.56
Male	94 (50)	
Female	94 (50)	
Active smoker, smoking <5 years ago	46 (24.5)	
Symptomatic	95 (50.5)	
Metastases at diagnosis	37 (19.7)	
Second primary	48 (25.5)	
Center of diagnosis (Hospital 1/2)		0.06
Overall	93/95 (49.5/50.5)	
Appendix	13/19 (40.6/59.4)	
Colon	15/13 (53.6/46.4)	
Lung	11/27 (28.9/71.1)	
Pancreas	14/4 (77.8/22.2)	
Small bowel	19/12 (61.3/38.7)	

Note: Wald test of comparison with the empty model was used to test for significance. 0.05 significance level is applied.

Abbreviation: SE, standard error.

3 | RESULTS

3.1 | Patient characteristics

In the total population of 434 patients, 188 patients with NET were identified of which 94 (50%) were male (Table 1). Tumors were located mainly in the digestive tract ($n = 120$, 63.8%), followed by lung ($n = 38$, 20.2%), unknown primary site ($n = 19$, 10.1%), urogenital ($n = 8$, 4.3%) and other locations ($n = 3$, 1.6%). A significant difference in age at diagnosis for tumor location was observed ($p < 0.001$). However, the interaction between gender and tumor location was not significant ($p = 0.65$, Supporting Information: Table 1A–C). Patients with appendiceal NET were younger than other tumor locations, respectively, a mean age of 41.3 and 64.0 years (Supporting Information: Table 2).

There was no significant difference in age between known and unknown tumor location ($p = 0.59$, Supporting Information: Table 3A,B). Tumor location did not differ between the two medical centers ($p = 0.06$, Table 1), except for pancreatic NET: almost 78% of all

TABLE 2 Pathology reports.

	Mean	95% CI	*p* value
Quality score (0–5)			<0.001
Overall	3.0	2.8–3.2	
Appendix	3.1	2.7–3.5	
Colon	3.3	2.9–3.7	
Lung	2.5	2.2–2.8	
Pancreas	3.2	2.7–3.7	
Small bowel	3.9	3.5–4.2	
Time APO–MTB (days)			
Overall	48.3	18.7–77.9	
Appendix	45.8	−10.8 to 102.4	
Colon	30.5	−45.4 to 106.4	
Lung	99.7	12–187.6	
Pancreas	13.5	−70.7 to 97.8	
Small bowel	50.6	−6.2 to 107.3	

Note: A linear model was applied with quality score as response and tumor location as main effect to test for significance. 0.05 significance level is applied.

Abbreviations: APO, pathology diagnosis; CI, confidence interval; MTB, first medical tumor board.

pancreatic NETs were diagnosed at Hospital 1 (Supporting Information: Table 4A,B).

Half of the study population ($n = 95$, 50.5%) presented with symptoms at the time of diagnosis. In 19.7% of the cases, patients presented with metastasis at time of diagnosis. In more than a quarter of the patients (25.5%), a second primary tumor was found.

3.2 | Pathology

Overall, a mean quality score of 3.0 was achieved in pathological reporting (Table 2). Only one pathology report, concerning a bronchial NET, had a score of 0. Of all remaining pathology reports, 6.9% scored 1 point, 29.3% scored 2 points, 29.3% scored 3 points, 24.5% scored 4 points and 9.6% scored 5 points. A significant difference in quality score between different tumor locations could be observed ($p < 0.001$, Supporting Information: Table 5A). Patients with small bowel NETs had a higher quality score (mean: 3.9) compared with all other tumor locations (Supporting Information: Table 5B). Hospital 1 had higher mean quality scores than Hospital 2 (3.16 [0.12] vs. 2.82 [0.12], $p = 0.0367$, Supporting Information: Table 6). A higher score corresponded with a better overall survival in univariate analysis ($p = 0.0035$, OR: 1.58, 95% confidence interval [CI] 1.16–2.16; Supporting Information: Table 7A). However, after correction for age, sex, WHO grading, and location in a multivariate regression, this could no longer be observed ($p = 0.1813$; Supporting Information: Table 7B).

The overall time between pathology (APO) diagnosis and the first *medical tumor board (MTB)* (time APO-MTB [TAM]) was on average 48 (15.06) days. Running pairwise *t* tests, only two tumor location group comparisons had a significantly different mean TAM (Supporting Information: Table 8A): unknown location versus esophagus and lung respectively. For tumors with unknown location, pathology was reported on average 23 (41.76) days *after* the first MTB. A shorter TAM did not correspond with a better overall survival ($p = 0.47$; OR: 1.002, 95% CI: 0.997–1.006, Supporting Information: Table 8B). No significant influence of TAM on disease progression could be observed ($p = 0.74$, Supporting Information: Table 8C).

3.3 | Diagnostics

In the total study, cohort 29.8% received a fluorodeoxyglucose or 68 Ga-DOTA-somatostatin analog PET-scan or somatostatin receptor scintigraphy (SRS). This was higher (61.3%) in case of unknown primary site. Patients with colorectal or appendiceal NET underwent nuclear imaging in, respectively, only 7.1% and 6.3% of cases. Hospital 2 performed more nuclear imaging compared with Hospital 1. This could be attributed to the percentage of lung NETs, respectively 66.7% and 50.0% (shown in Table 3).

Other imaging (ultrasonography, X-ray, computerized tomography [CT], and/or magnetic resonance imaging; Figure 1) was performed in 74.5% of the patients. Nearly 85% of the patients with an unknown tumor location underwent one of the latter. Almost three quarter of the patients with gastric NET did not receive any kind of imaging and diagnosis was mainly based on endoscopy. No relationship between diagnostic imaging and overall survival ($p = 0.067$), neither progression free survival ($p = 0.32$) could be observed Supporting Information: Table 9A,B).

3.4 | Therapy

In total, 81.4% ($n = 153$) of the patients received therapeuti interventions. Table 4 shows the first-line therapy according to tumor location. The time between diagnosis and first treatment was on average 12 (13.62) days.

TABLE 3 Use of diagnostic modalities.

	Nuclear (PET/SRS) (%)	Imaging (US/X-ray/CT/MRI) (%)
Tumor location		
Overall	29.8	74.5
Appendix	6.3	71.1
Colon	7.1	67.9
Lung	65.3	88.2
Pancreas	44.5	83.3
Small bowel	17.1	93.2
Hospital 1/2		
Overall	23.7/35.8	75.3/73.7
GEP-NETs	13.6/14.8	74.2/72.2
Lung	50.0/66.7	83.3/81.5

Abbreviations: CT, computerized tomography; GEP-NET, gastroenteropancreatic neuroendocrine tumor; MRI, magnetic resonance imaging; PET, positron emission tomography; SRS, somatostatin receptor scintigraphy; US, ultrasonography.

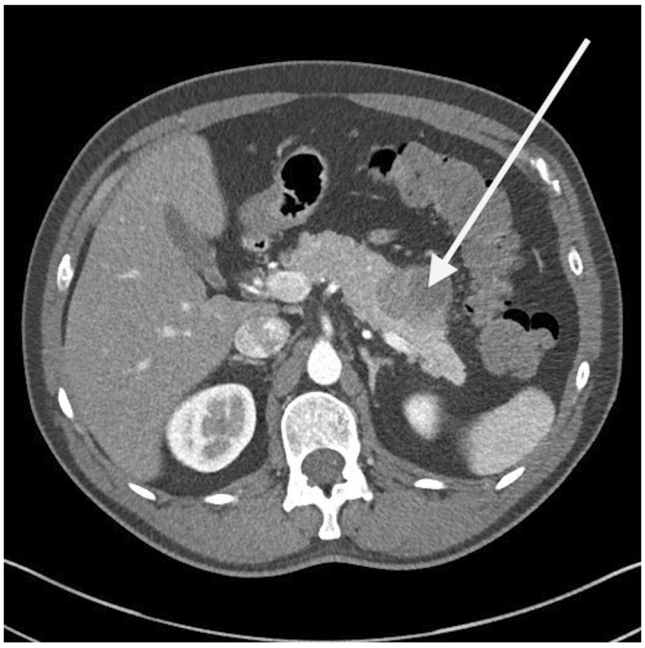

FIGURE 1 Computed tomography of the abdomen (arterial phase) showing a pancreatic neuroendocrine tumor (arrow).

Overall, 3 out of 5 patients ($n = 126$) underwent surgery, followed by medical therapy in 31.8% ($n = 41$), chemotherapy in 15.4% ($n = 29$), and radiotherapy in 6.4% ($n = 12$).

Second-line therapy was administered in almost one-third of the patients ($n = 43$, 28.1%) of which more than half received medical therapy as treatment of choice ($n = 23$, 53.5%).

Tumor location was significantly associated with the use of surgery ($p = 0.004$) or chemotherapy ($p = 0.048$) as first-line therapy. Most GEP-NETs received surgery as first-line therapy (90/120, 75.0%), with the exception of esophageal NET which primarily received chemoradiotherapy.

Only 10.5% of patients received adjuvant chemotherapy. In patients who received chemotherapy as first-line therapy, medical therapy (e.g., somatostatin analogs) was associated with 53.4%. More than 85% of patients that received first-line radiotherapy also received concomitant chemotherapy.

There was no association between overall survival or progression-free survival and time between first medical tumor board and start of therapy ($p = 0.79$ and $p = 0.84$, respectively).

3.5 | Survival

In total, 49 patients (26.1%) had died of which 45 due to their NET and 4 due to other causes. Eleven patients (5.9%) had progressive disease, in 39 patients (20.7%) stable disease could be observed and 50 patients (26.6%) were in remission. Sixteen patients (8.5%) had no evidence of disease. Twenty-three patients (12.3%) survival data could not be retrieved.

Median overall survival was 362 days (468) (range: 12–2161 days) and 74% of the population was alive at the end of follow-up. The median overall survival was not reached in this study (Figure 2).

A significant association between overall survival and tumor location ($p = 0.013$; Figure 3; Table 5) and symptoms at diagnosis ($p = 0.008$) could be observed. Referral from the general practitioner ($p = 0.69$) or number of therapies ($p = 0.10$) were not associated with a change in overall survival.

4 | DISCUSSION

4.1 | Patient characteristics

We found most NETs to be located in the digestive (63.8%) and respiratory (20.2%) systems. A similar distribution was found in other studies [21, 22] with 62%–67% gastrointestinal NETs (GEP-NETs) and 22%–27% bronchopulmonary NETs (BP-NETs); however, Helland et al. found a higher percentage of small bowel NETs (53%).

A mean age of 60 years (range 9–89 years) at diagnosis was similar to other studies with a significantly

TABLE 4 First-line therapy according to tumor location and effect of tumor location on choice of first-line therapy.

	1st line surgery	1st line chemoRx	1st line radioRx	1st line medical Rx	No therapy
Overall	65.4%	6.9%	3.7%	6.4%	17.6%
Tumor location					
Appendix ($n = 32$)	31 (96.9%)	0	0	0	1 (3.1%)
Colon ($n = 28$)	23 (82.1%)	0	0	0	5 (17.9%)
Lung ($n = 38$)	23 (60.5%)	4 (10.5%)	3 (7.9%)	0	8 (21.1%)
Pancreas ($n = 18$)	9 (50%)	3 (16.7%)	1 (5.6%)	3 (16.7%)	2 (11.1%)
Small bowel ($n = 31$)	25 (80.6%)	0	0	2 (6.5%)	4 (12.9%)
p value	0.004	0.048	0.197	0.014	

Note: Logistic regression was applied given a certain first-line therapy as response and tumor location as main effect. *F* test was applied to test if the effect of tumor location on a certain first-line therapy is significant. 0.05 significance level is applied.

Abbreviation: Rx, therapy.

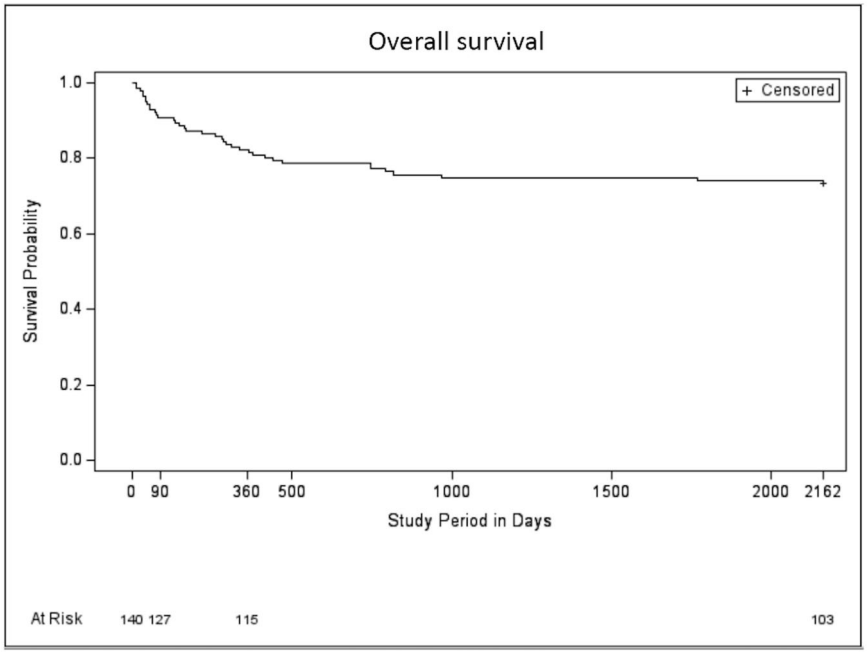

FIGURE 2 Accelerated failure time model for the overall cohort

lower age for appendiceal NETs as well [23]. The presence of metastasis in 19.7% of patients at the time of diagnosis was also similar to the literature ranging from 12% to 23% [21, 22].

We observed a difference in the incidence of pancreatic NETs in between hospitals. This could be explained by the implementation of expert centers for complex tumors. This resulted in an allocation of pancreatic tumors to one center and esophageal tumors to the other.

Half of the study population experienced nonspecific symptoms at the time of diagnosis. This was also the case in other studies [21], where most of the diagnoses were made on technical investigations for nonspecific symptoms or during surgery for various other reasons. On the other hand, only 2.1% of our patients experienced a typical neuroendocrine syndrome. This incidence is substantially lower than what could be found in literature [24] with up to 13% of small bowel NETs (in the presence of liver metastases) and 30% of pancreatic NETs presenting with endocrine symptoms. We believe our findings could be explained by the retrospective nature of this study and consequently less adequate documentation of symptoms rather than an absolute

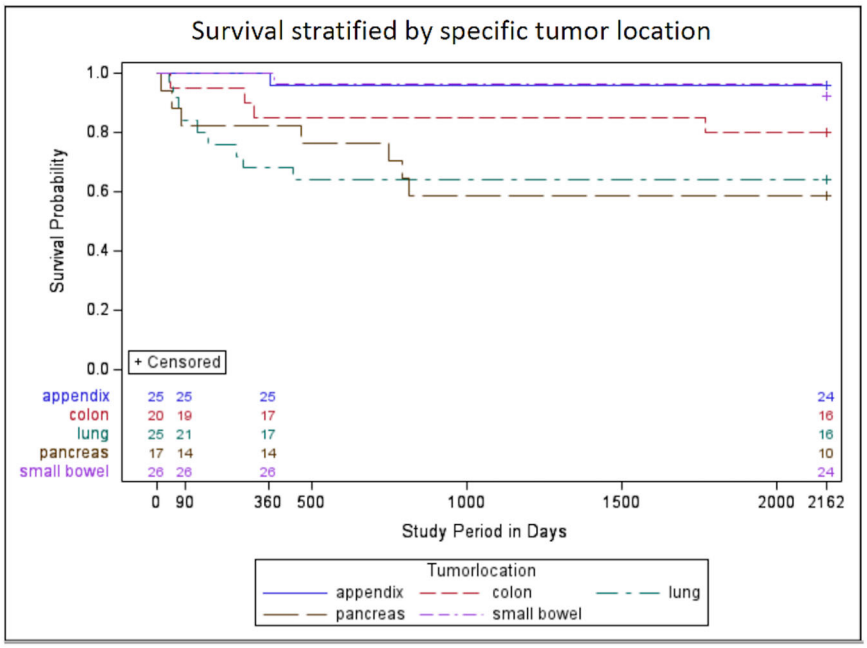

FIGURE 3 Accelerated failure time model for the most important tumor locations.

TABLE 5 Association between overall survival and respective tumor location, referral from general practitioner, presence of symptoms and number of therapies.

Effect	DF	Wald χ^2	*p* value
Tumor location	8	19.2971	0.0133
Referral by GP	1	0.1612	0.6881
Presence of symptoms	1	7.1217	0.0076
Number of therapies	1	2.6845	0.1013

Note: Survival analysis was based on the original data using accelerated failure time model. The Type III Anova test was used to test the association. 0.05 significance level is applied.

Abbreviations: DF, degrees of freedom; GP, general practitioner.

difference in the presence of a neuroendocrine syndrome. Only 26.3% of symptomatic tumors were metastatic at diagnosis.

Selection bias may play a role in some of the findings of our study. We subtracted our data from pathology records linked to the national cancer registry to reduce this potential bias to a minimum. However, because we obtained our data from regional hospitals, we could not exclude center bias.

In 25.5% of patients, a synchronous or metachronous second primary malignancy (SPM) could be diagnosed. Patients with a GEP-NET were diagnosed with an SPM more frequently. This is a slighter higher proportion than described in literature, ranging from 9.8% to 18.9% [25–27]. This can be explained by the fact that we included all patients with an SPM, whilst other studies excluded patients with any genetic predisposition syndrome.

4.2 | Pathology

In general, pathology reports had a mean quality score of 3 out of 5, with small bowel NETs scoring significantly higher with 3.9 ($p < 0.02$). This can be explained by the higher specialist awareness for NETs in the case of small bowel tumors. In Belgian clinical practice, surgeons are more likely to request Ki67 in case of small bowel tumors than for colorectal carcinomas since colorectal NETs are uncommon, comprising less than 1% of all colorectal cancers [28]. The lower quality score of BP-NETs according to our scoring system can be explained by the fact that Ki67 was not a criterium for grading of BP-NETs back in 2015 [29]. Another explanation could be the lower exposure of pulmonary pathologists to NETs, given its low incidence in pulmonary malignancies.

The importance of a qualitative pathology report was confirmed by the ENETS in 2017, in which they proposed a list of minimal requirements, including Ki67-index, to allow proper differentiation and to be able to compare different studies [30]. Perren et al. stated that Ki67 was more accurate to assess tumor grade than mitotic count. Similarly, Jann et al. [31] showed that TNM staging and grading are the main parameters to identify

prognostically distinct subgroups in GEP-NETs. So far no consensus exists on the prognostic role of Ki67 in BP-NETs due to lack of evidence [32, 33]. Nonetheless, Ki67 is often required by oncologists for therapy planning [33].

Pathologists should remain prudent to use NET-specific TNM staging, since using TNM staging for adenocarcinoma may lead to incorrect therapy and assessment of prognosis. As other studies propose, both histopathologic and clinical parameters should be combined for risk stratification to determine treatment strategies for these patients.

4.3 | Diagnostics

According to the ENETS consensus guidelines of 2016, SRS or preferably PET should be part of the tumor staging preoperative imaging and restaging process, particularly in high-grade tumors or when metastatic disease is suspected. In our study, 29.8% of cases underwent a PET or SRS, which can be explained by a large portion of appendiceal NETs and low-grade NETs. Additionally, one center did not have a PET scan at their disposal, and it was not common practice to perform a PET-CT for gastrointestinal tumors, even in case of unknown origin. In case of appendiceal NET it is not necessary to perform nuclear imaging when Ki67 is low [34, 35]. The opposite is true for pulmonary tumors, where it is common practice to perform PET-CT [36]. This resulted in a significant higher number of PET-CTs in pulmonary NETs. The low incidence of imaging in gastric NETs can be explained by the fact that most diagnoses were made early based on endoscopy and endoscopic ultrasonography. Indeed, only when there is a risk of metastases, extensive imaging must be performed [5]. Nevertheless, given endoscopy's moderate sensitivity for locating primary tumors and its inability to detect distant metastases, imaging remains crucial to establish the extent of disease in advanced neoplasms and in type 3 NENs [11, 37].

4.4 | Therapy

In general, local NETs are more often treated with surgery and/or surveillance, whereas advanced stage or metastatic NETs require a more patient-tailored approach with a combination of surgery, systemic therapy and radiotherapy.

Almost all appendiceal NETs were surgically resected since most appendiceal NETs are incidental findings. Of colorectal and small bowel NETs, 81% got resected. There are several surgical options for small bowel NETs and even in the case of unresectable disease, resection of the primary tumor may avert gut obstruction [38]. Rectal NETs are relatively indolent in nature and an incidental finding in which the risk of lymph node metastasis is the most important factor in surgical strategy. Also, colon NETs are usually diagnosed either at biopsy of a mass or after surgical resection [39]. They behave more aggressively than rectal NETs and recommendations considering surgical strategies have yet to be elaborated [40]. In our population, we grouped colon and rectal NETs together.

We grouped typical carcinoid tumor, atypical carcinoid tumor, and large cell neuroendocrine carcinoma together as BP-NETs. Of BP-NETs, 60% got resected. None of the resected tumors and less than half of non-resected NETs had metastases at diagnosis. Whether surgery is applied and the choice of surgical technique depends on the type of BP-NET and tumor stage [41].

Given their heterogeneity and diverse presentation, it remains difficult to standardize treatment strategies. Therefore, treatment should be discussed and determined in a multidisciplinary tumor board to improve treatment efficiency and clinical outcome [42–44]. Hence, we assessed time from pathology to first multidisciplinary tumor board (TAM) as a parameter of quality of care. We could not observe a significant correlation between TAM and disease-free survival or overall survival ($p > 0.05$). However, we believe this could be a result of a relatively small patient population making it harder to detect marginal differences.

The wide range of therapeutic options, especially systemic therapy, is rapidly evolving. Nowadays, patients can receive somatostatin analogs (SSAs), mammalian target of rapamycin (mTOR) inhibitors, cytotoxic chemotherapy, peptide receptor radionuclide therapy (PRRT) or vascular endothelial growth factor (VEGF) pathway inhibitors, which further allows for a more patient- and tumor-tailored approach [45]. In the future, therapy can be supported and largely guided by epigenetic characterization of NETs [46], making tumor localization as a marker for therapy possibly less important. This again highlights the importance of an elaborate and correct histopathologic evaluation.

4.5 | Outcome

The overall 5-year survival rate was 74.29% for all NETs regardless of site, which corresponded to findings in literature [47]. Overall mortality was significantly related to tumor location with the highest death rates for pancreatic NETs and the lowest for appendiceal NETs, comparable to other studies [48]. According to Dasari et al., survival for NETs has improved over time, reflecting improvement in diagnosis and therapy [1].

The Belgian healthcare system offers low-threshold services in terms of access to practitioners, diagnostics,

and treatment. Therefore, the socioeconomic status was not taken into consideration when evaluating survival in this study.

5 | CONCLUSION

This 6-year analysis of NETs provides epidemiological information as well as insights in clinical practice and quality of pathology reports of two large regional Belgian hospitals. Overall, epidemiological results were comparable with findings in literature. Gastrointestinal NETs met most of the requirements of qualitative pathology reporting and diagnostic imaging as listed in the ENETS consensus guidelines. However, consensus with regard to bronchopulmonary NETs is still scarce and remains an objective for future research.

Given the heterogeneity and diverse presentation of NETs, treatment strategies should be discussed in specialized multidisciplinary tumor boards in the presence of a dedicated pathologist, oncologist, and surgeon. This could prevent unnecessary referral to tertiary centers and would facilitate regional care in these patients, despite the rarity of the disease.

AUTHOR CONTRIBUTIONS

Hannah Bloemen: Formal analysis (lead); writing – original draft (lead); writing – review and editing (lead). **Kristien Kneepkens**: Writing – original draft (equal); writing – review and editing (supporting). **Karen Deraedt**: Data curation (equal); writing – review and editing (equal). **Anna Ivanova**: Formal analysis (equal); writing – review and editing (supporting). **Gregory Sergeant**: Conceptualization (equal); data curation (equal); funding acquisition (equal); methodology (equal); project administration (equal); supervision (equal); writing – review and editing (equal). **Jeroen Mebis**: Conceptualization (equal); data curation; funding acquisition (equal); methodology (equal); project administration (equal); supervision (equal); writing – review and editing (equal). **Kurt Van der Speeten**: Conceptualization (equal); data curation; funding acquisition (equal); methodology (equal); project administration (equal); supervision (equal); writing – review and editing (supporting).

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

This study was approved by the institutional review board and ethics committee (approval ID CME2015/620), conform national privacy legislation and conducted according to the revised version of the Declaration of Helsinki.

INFORMED CONSENT

The need for informed consent was waived given the retrospective character of the study.

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